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Biomechanical Acclimation: Flying Cold

Why are animals reared at colder temperatures larger? A new study shows that fruit flies reared at lower temperatures are better able to fly in the cold.

Joel G. Kingsolver
and Tyson L. Hedrick

The temperature–size rule describes one of the most common patterns of phenotypic plasticity in nature: in most species, individuals reared at lower temperatures have increased adult body sizes [1]. A variety of adaptive and non-adaptive hypotheses for the temperature–size rule have been proposed, but a general explanation remains elusive [2,3]. Bergmann's rule describes a distinct but related empirical pattern found in many animal taxa: populations or species that occur in colder environments have evolved relatively larger adult sizes [4]. Many *Drosophila* follow both of these rules [5,6]. Why are flies reared at colder temperatures larger? Why do flies living in colder environments evolve larger size?

The clue to addressing these questions for flies may lie in the allometric scaling of different aspects of size. In populations of *Drosophila subobscura* on three continents, lower developmental temperatures generate large increases in wing length and wing area, but more modest changes in body mass; as a result, flies reared at lower temperatures have substantially reduced wing loading — that is, body mass/wing area ratio [5]. Gilchrist and Huey [5] suggested that this plastic response in morphology is biomechanically adaptive: reduced wing loading could facilitate flight at colder temperatures where the mechanical power output of flight muscles is reduced.

A recent study by Frazier *et al.* [7] provides an experimental test of this hypothesis in *Drosophila melanogaster*. As in earlier studies, the authors found that *Drosophila melanogaster* reared at lower temperatures had a larger wing area relative to their body size, reducing the amount of mass that must be supported by a given unit of wing. Furthermore, wing length also increased relative to body mass, even after accounting for the increase in total

wing area. This suggests that the second moment of area of the wings [8], a measure of wing shape and the best morphological predictor of slow flight capability, also increased relative to body mass.

Many factors other than wing area and length contribute to flight performance, however, so positive allometric scaling of these wing parameters is not proof of actual capability. Frazier *et al.* [7] tested flight performance directly by eliciting take offs from flies reared over a range of temperatures. Virtually all flies were able to take off at warmer environmental temperatures (18°C), but only flies reared at the coldest temperature in the study (15°C) were able to take off when the environmental temperature was reduced to 14°C. Thus, not only do flies reared at cooler temperatures have the biomechanical equipment for efficient low speed flight, they exhibit improved flight performance.

The study [7] indicates that development plasticity to cold rearing temperatures may be beneficial to flies by increasing flight performance at cold temperatures. A full demonstration of the beneficial plasticity hypothesis, however, would require evidence that flies reared at high temperatures have increased performance at high temperatures [9,10]. Why do flies reared at higher temperatures have relatively

smaller wings? Intriguingly, flies reared at lower temperatures also had a lower wingbeat frequency, a factor which should reduce forward flight speed and other aspects of flight performance. Whether this possible tradeoff provides the basis for beneficial plasticity in this or other insects will require further study.

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Axonal Domains: Role for Paranodal Junction in Node of Ranvier Assembly

A new study shows that communication between axons and glia at the paranodal junction can orchestrate the formation of the node of Ranvier.

David A. Lyons* and William S. Talbot

In the vertebrate nervous system, myelin facilitates the rapid conduction of neural impulses. Consecutive segments of myelin along the length

of an axon are separated by short unmyelinated domains, called nodes of Ranvier, which contain a high concentration of voltage-gated sodium channels that propagate the neuronal impulse. Each node of Ranvier is

flanked on either side by a domain called the paranode (Figure 1A), which is a site of tight contact between the myelinating glial cell and the axon. Recently, the debate regarding whether the organization of these axonal domains is driven primarily by interactions between axons and glia at the paranode, or by mechanisms that determine the position of the node independent of the paranode, had swung strongly in favour of the latter [1–4]. A new study, published in the *Journal of Cell Biology*, however, suggests that a key component of the paranode, neurofascin 155 (Nf155), can orchestrate the formation of the node of Ranvier and regulate growth of myelinating processes along axons in the central nervous system (CNS) [5]. These results may be relevant to our understanding of the pathophysiology of multiple sclerosis, as disruption of paranodal Nf155 has been associated with the onset of demyelination in this disease [6].

The L1 immunoglobulin cell-adhesion molecule (Ig-CAM) family member neurofascin is required for the normal localization of key proteins at both the node of Ranvier and the paranode [4,5]. Two neurofascin isoforms are important for the development of myelinated axons. The neuronal isoform neurofascin 186 (Nf186) localizes to the node of Ranvier, whereas Nf155 is expressed in myelinating glia at the paranodal junction. Paranodal Nf155 binds to contactin, another Ig-CAM expressed on the axonal surface [7]. Contactin forms a complex with a neuixin-like molecule in the axon called Caspr [7], and this adhesion complex can stimulate rearrangement of the axonal cytoskeleton in response to axon–glia contact (reviewed in [8,9]). Mice that lack either Caspr or contactin have disrupted axon–glia junctions at the paranode, but a normal localization of sodium channels at the early node of Ranvier [1,2]. Over time, the integrity of the node of Ranvier is affected in these and other mutants that disrupt the axon–glial paranodal junction, such that sodium channels initially clustered at the node disperse somewhat along the length of the axon [1–3,10,11]. Together these results suggested that the paranodal axon–glial junction plays a role in maintaining the integrity of the node of Ranvier, but not in the initial

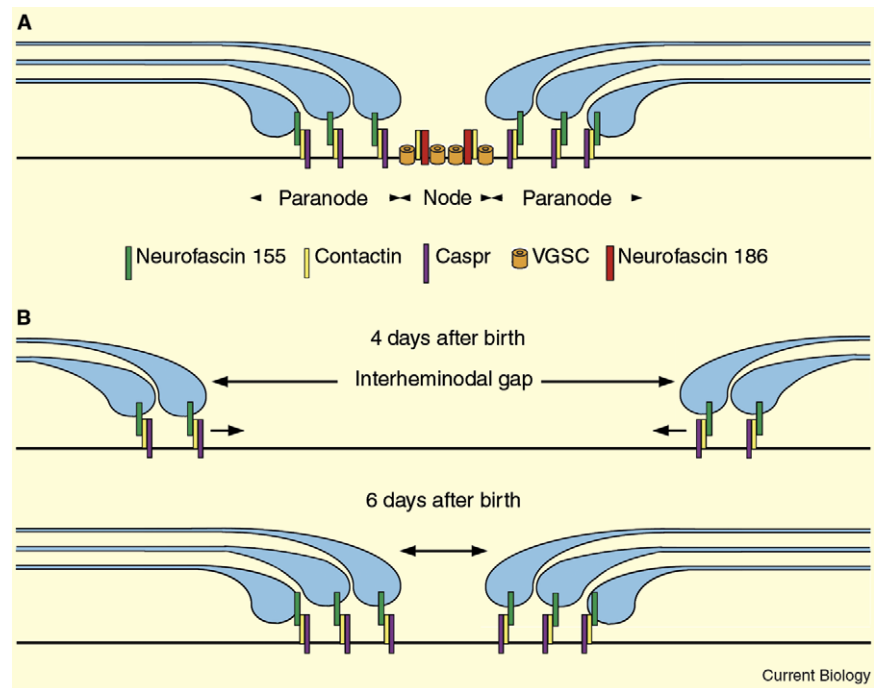


Figure 1. The node of Ranvier in the central nervous system.

(A) Paranodes in the CNS contain myelinating glial neurofascin 155 (green) and axonal Caspr (purple) and contactin (yellow). The node contains a high density of voltage-gated sodium channels (VGSC, orange) and neurofascin 186 (red). Transient expression of contactin at the node may also increase the expression of sodium channels there [19]. Oligodendrocyte processes are depicted in blue. (B) Myelinating oligodendrocyte processes (blue) begin to wrap axons before they extend fully along the length of the axon, thus leaving large 'interheminodal gaps' between consecutive processes. Nf155 (green) is localized to the growing tips of these processes and colocalizes with axonal contactin (yellow) and Caspr (purple). Nf155 is required for this gap to be refined at the normal rate, which normally occurs between 4 and 6 days after birth, but it is unclear whether this is mediated through interaction with Caspr and contactin. Large interheminodal gaps have not been reported during Schwann cell myelination (not shown).

localization of sodium channels and other proteins to the node of Ranvier. Previous analysis of neurofascin also argued against a role for paranodal Nf155 in the initial assembly of the node of Ranvier. Neurofascin-null mutants that lack all neurofascin isoforms do not correctly localize proteins to the node or paranode. In the peripheral nervous system (PNS), the overexpression of Nf155 in peripheral myelinating glia (Schwann cells) of neurofascin-null mutants was sufficient to reconstitute the paranodal junction complex but was not sufficient to localize sodium channels to nodes [4]. These studies implied that another neurofascin isoform, most likely neuronal Nf186, is required for node of Ranvier formation. This hypothesis is now supported by the recent observations of Zonta *et al.* [5], which show that Nf186 can localize sodium channels to the node when it is overexpressed

and targeted to the node in the CNS and PNS of neurofascin-null mutants. Collectively, these data lowered expectations that the paranodal junction, and glial Nf155 in particular, play a significant role in the initial assembly of the node of Ranvier.

In a striking finding, however, Zonta *et al.* [5] show that overexpression of Nf155 in myelinating glia of the CNS (oligodendrocytes) in the neurofascin-null mutant can restore sodium channel localization to the nodes of Ranvier. This result demonstrates that the reconstituted paranodal axon–glial junction in the CNS is sufficient to organize the node of Ranvier in the absence of all other neurofascin isoforms, including Nf186. These data indicate that Nf186 is not required for the initial clustering of sodium channels at nodes of Ranvier in the CNS. Another notable finding is that Nf155 regulates the growth

of myelinating processes of oligodendrocytes along axons in the CNS. During early stages of myelination, oligodendrocyte processes begin to wrap axons before they extend fully along the length of the axon [12,13]. At 4 days after birth, Zonta *et al.* [5] visualize large segments of axon that are left bare as adjacent oligodendrocyte processes grow towards one another to form consecutive myelin segments (internodes). Nf155 is expressed at the leading tips of converging processes even when they are separated by a large distance. This leading edge Nf155 also colocalizes with axonal contactin and Caspr, suggesting that the paranodal junction may form in early growing processes. By 6 days after birth, wild-type mice and neurofascin-null mutants with Nf155 overexpressed in myelinating glia have very few large unmyelinated gaps, whereas neurofascin-null mutants with or without neuronal Nf186 still have unmyelinated gaps about five times as large as wild type at this stage [5]. Therefore, Nf155 supports the normal growth of myelinating processes along the length of the axon. It would be interesting to monitor the rate of convergence of myelinating processes in Caspr and contactin mutants to see whether the Nf155–contactin–Caspr paranodal junction complex functions during this process. It is possible that Nf155 might interact with other proteins during the growth of myelinating processes, independent of its ability to cluster nodal proteins.

The results of Zonta *et al.* [5] pose the question of how the CNS paranodal junction might function to cluster proteins at the CNS node. One proposal is that the paranodal junction could act as a diffusion barrier [11,14] that restricts the movement of membrane proteins, like sodium channels, along the axon until the converging paranodes meet to form the node. The co-localization of Nf155 with contactin and Caspr in converging processes suggests the formation of early paranodal junctions. The fact that Nf155 is required for the growth of myelinating processes and that it can cluster proteins at the node supports the possibility that movement of these early paranodal junctions along the axon might cluster sodium channels at the node. Alternatively, the

paranodal junction complex might localize nodal proteins through an indirect mechanism mediated by rearrangement of the axonal cytoskeleton [8,9].

The question also remains regarding why the paranodal junction in the PNS cannot localize proteins to the node of Ranvier. One might have expected the role of the myelinating glial cell to be similar in the PNS and CNS, given that Schwann cells can restore nodal protein localization during remyelination of CNS axons [15]. However, myelinating glial Nf155 is not sufficient to cluster nodal sodium channels in the PNS [5]. The explanation may lie in intrinsic differences in the interactions between axons and glia in the PNS and CNS. Unlike oligodendrocytes, Schwann cells extend along the majority of the length of the presumptive internode, in the absence of Nf155 and before committing to myelination [5,16]. Indeed, many Schwann cells that migrate and extend along axons do not myelinate [16], emphasizing that the extension of glial processes is not as tightly coupled to myelination and paranode formation in the PNS as in the CNS. Instead, it seems that neuronal Nf186 plays the predominant role in the assembly of sodium channel clusters at peripheral nodes by virtue of its interaction with the axonal cytoskeleton [5,8,9]. Cell culture analyses suggest that gliomedin [17,18], a protein that binds Nf186 and is secreted by Schwann cells, can cluster Nf186 in peripheral axons. Zonta *et al.* [5] also demonstrate that Nf186 can reconstitute nodal proteins when targeted to the node in the CNS, but it is unclear how clustering of Nf186 relates to the growth of myelinating oligodendrocyte processes; also, the mechanisms that might localize Nf186 to the CNS node are unknown.

In conclusion, the results of Zonta *et al.* [5] provide compelling new evidence for a role of the paranodal Nf155 in clustering sodium channels at the node of Ranvier in the CNS. Zonta *et al.* [5] also draw attention to another poorly understood aspect of myelinated axon development — internode growth. They provide evidence that early internode growth is regulated, at least in part, by Nf155, but the mechanisms that regulate the long-term growth of myelinating internodes in the CNS

are almost completely mysterious. Continued analyses of the mechanisms that assemble the node of Ranvier and promote myelin growth will help us to understand processes that may be central to the repair and restoration of the function of myelinated axons damaged by injury or disease.

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